ORGANIC
LETTERS

2006
Vol. 8, No. 4
669−672

Regio- and Diastereoselective Reductive Coupling of Vinylepoxides Catalyzed by Titanocene Chloride

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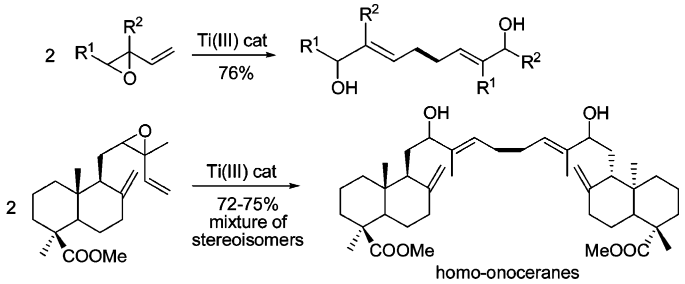
Received November 24, 2005

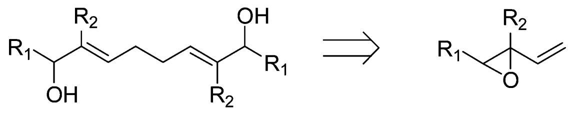
ABSTRACT



The Ti(III)-catalyzed reaction of a series of vinylepoxides leads, with regio- and *E*-diastereoselectivity control, to good-to-excellent yields of the corresponding homocoupling products. This homocoupling reaction, which involves a new C–C bond-forming method, takes place via a S_N2' process between an allyltitanium species and the starting vinylepoxide. The process can be used for the rapid and efficient formation of highly valuable intermediates for organic synthesis, as well as new interesting homologues of natural products.

The structural unit 2,7-dimethylocta-2,6-diene is included in a number of terpenoids belonging to the families of triterpenes and carotenes.[1] In this context, 2,7-dimethylocta-2,6-dien-1,8-diol (**1**) has been widely used as a central building block for the synthesis of squalene-derived polyethers with potent cytotoxic activities, such as teurilene, glabrescol, thyrsiferol, venustratiol, longilene peroxide, etc. (Scheme 1).[2]

Scheme 1



1: R_1 = H, R_2 = Me

2: R_1 = H, R_2 = Me

To date, low yields of **1** have been prepared as a mixture of stereoisomers via isoprene dimerization[3] or, at 30% overall yields, in four steps from tiglic acid using Franck's protocol.[4]

On the basis of the reductive coupling of terpenic allylic halides catalyzed by Cp_2TiCl,[5] which leads, with high yields and selectivities, to the corresponding α,α′ coupling products via allyltitanium species (Scheme 2, pathway a), we surmised that structures such as **1** could be efficiently prepared via the Cp_2TiCl-mediated homolytic opening of vinyloxiranes[6a−c] (Scheme 1). Thus, the exposure of vinyloxiranes to catalytic

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(1) *Dictionary of Terpenoids*; Connolly, J. D., Hill, R. A., Eds.; Chapman & Hall: London, U.K., 1991; Vol. 2, p 1405.

(2) (a) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *J. Org. Chem.* **1990**, *55*, 5088−5107. (b) Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *J. Org. Chem.* **1991**, *56*, 2229−2311. (c) Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **1999**, *121*, 6792−6797. (d) Morimoto, Y.; Kinoshita, T.; Iwai, T. *Chirality* **2002**, *14*, 578−586. (e) Morimoto, Y.; Iwai, T.; Nishikawa, Y.; Kinoshita, T. *Tetrahedron: Asymmetry* **2002**, *13*, 2641−2647. (f) McDonald, F. E.; Wei, X. *Org. Lett.* **2002**, *4*, 593−595.

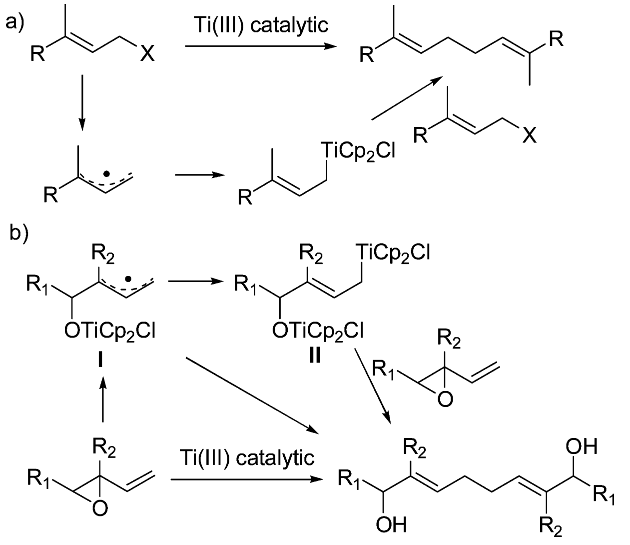
(3) (a) Brossas, J.; Pinazzi, C. P.; Clouet, F. *J. Polym. Sci., Part A: Polym. Chem.* **1973**, *11*, 1517−1529. (b) Watanabe, S.; Suga, K.; Watanabe, T. *Chem. Ind.* **1970**, 1145.

(4) Lindel, T.; Franck, B. *Tetrahedron Lett.* **1995**, *36*, 9465−9468.

(5) Barrero, A. F.; Herrador, M. M.; Quílez del Moral, J. F.; Arteaga, P.; Arteaga, J. F.; Piedra, M.; Sánchez, E. *Org. Lett.* **2005**, *7*, 2301−2304.

10.1021/ol052849w CCC: $33.50

Scheme 2



Ti(III) in the presence of an excess of TMSCl/collidine (a combination previously reported to regenerate starting Ti(IV) species from titanium alcoxides)[6d] would afford the corresponding β-titanoxy radical **I**, which would then evolve toward an allyltitanium species **II** (an intermediate similar to that postulated for allylic halides). The latter, acting as a soft nucleophile, would finally add to a second molecule of the starting vinyloxirane via a S_N2' process (Scheme 2, pathway b).

Nucleophilic addition to vinylepoxides has been quite extensively studied, and it transpires that the outcome of the reaction depends on the degree of hardness of the nucleophile.[7] Within this context, palladium complexes have been reported to promote coupling reactions between vinyloxiranes and nucleophiles to give excellent yields of predominantly S_N2' products.[8] Recently, the copper-catalyzed enantioselective conjugate addition of trialkylaluminum reagents to vinylepoxides using chiral phosphorus-based ligands has been reported.[9]

We describe here the results of our initial experiments with the coupling reaction of vinyloxiranes when treated with catalytic Cp_2TiCl. Two works on the subject have already been published: thus, Yadav et al. used an excess of Ti(III) to reduce internal vinylepoxides to the corresponding allylic alcohols, to convert terminal vinylepoxides into conjugate dienes and to synthesize butadienyl alcohols via the deoxygenation of epoxyallylic alcohols.[10]

We started our study by making commercial vinyloxirane **4** react with 0.2 equiv of Cp_2TiCl_2 and Mn in excess (8 equiv) in the presence of 4 and 7 equiv of TMSCl and collidine, respectively.

Under these conditions, the reaction took place rapidly and after 10 min a 66% yield of γ,γ' coupling product **5** together with minor quantities of the γ,α' regioisomer **6** were obtained (Table 1, entry 1). The reaction also proved to be completely diastereoselective, with only *E* isomers being obtained.

Table 1. Homocoupling Processes of Vinylepoxides in the Presence of Catalytic Cp_2TiCl

entry	substrate	Cp_2TiCl_2/Mn (equiv)	*c* (M)	time (min)	product[a]	yield (%)	ratio $\gamma,\gamma':\gamma,\alpha'$
1	**4**	0.2/8	0.1	10	**5** + **6**	88	3:1
2	**2**	0.2/8	0.1	10	**1** + **3**	92	6:1
3[b]	**2**	0.2/8	0.1	60	**1** + **3**	52	5:1
4[c]	**2**	0.2/8	0.1	17	**1** + **3**	93	5.5:1
5	**7**	0.2/8	0.1	15	**8** + **9** + **10**	75	1:0
6	**11**	0.2/8	0.1	15	**8** + **9** + **10**	72	1:0
7	**2**	0.2/8	1	10	**1** + **3**	87	6:1
8	**2**	0.2/8	0.01	10	**1** + **3**	90	6:1
9[d]	**2**	0.2/8	0.05	70	**1** + **3**	91	5:1
10	**2**	0.01/8	0.1	50	**1** + **3**	89	5:1
11	**2**	0.01/4	0.1	50	**1** + **3**	92	5:1
12	**11**	0.01/8	0.1	50	**8** + **9** + **10**	75	1:0
13	**12**	0.2/8	0.1	15	**13** + **14**	88	2:1

[a] In most cases, the different isomers obtained in each homocoupling process were isolated either by column chromatography on $AgNO_3$ (15%)/Si gel or by HPLC. For details, see Supporting Information. [b] Reaction carried out at 0 °C. [c] Reaction carried out using 10 mmol of substrate. [d] Reaction carried out in the presence of 20 equiv of acrylonytrile.

Having efficiently achieved the homocoupling of the vinyloxirane **4**, we subjected 1,2-epoxyisoprene, **2**, to the same experimental conditions to prepare the valuable synthetic intermediate **1**. The hoped-for conversion took place efficiently, with a 76% yield of **1** being obtained as a result of a γ,γ' coupling process (entry 2). An additional 16% of the γ,α' isomer **3** was isolated. Like that with vinyloxirane, the reaction was completely diastereoselective toward *E* olefins. An increase in the regioselectivity of the process was also noted. No higher regioselectivity was obtained when the reaction was carried out at 0 °C; instead, a decrease in the reaction rate was observed (entry 3).

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(6) The methodology for the homolytic opening of oxyranes using stoichiometric Ti(III) was initially established by: (a) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986−997. For catalytic protocols, see: (b) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849−12859. (c) Gansäuer, A.; Lauterbach, T.; Narayan, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5556−5573. (d) Justicia, J. J.; Rosales, A.; Oller-López, J. L.; Valdivia, M. V.; Haïdour, A.; Oltra, J. E.; Barrero, A. F.; Cárdenas, D. J.; Cuerva, J. M. *Chem.−Eur. J.* **2004**, *10*, 1778−1788.

(7) (a) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323−2367. (b) Restorp, P.; Somfai, P. *Chem. Commun.* **2004**, *18*, 2086−2087.

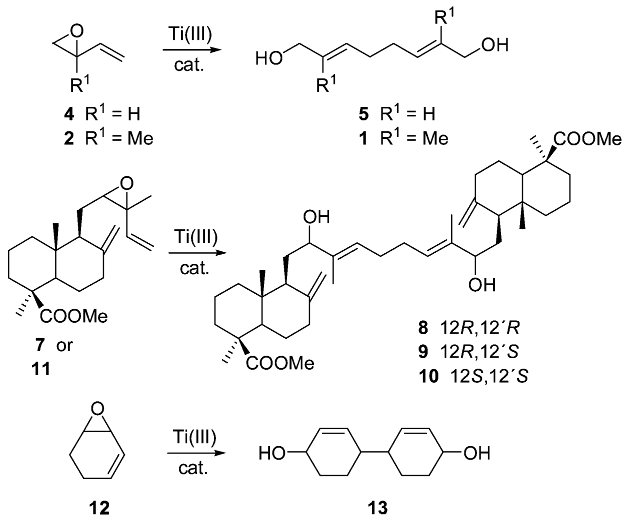
(8) (a) Tsuji, J. In *Palladium Reagents and Catalysts*; Wiley: Chichester, U.K., 1995. (b) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 4, pp 585−661. For some recent examples, see: (c) Nanayakkara, P.; Alper, H. *J. Org. Chem.* **2004**, *69*, 4686−4691. (d) Castaño, A. M.; Méndez, M.; Ruano, M.; Echavarren, A. *J. Org. Chem.* **2001**, *66*, 589−593. (e) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968−5976. (f) Trost, B. M.; Ceschi, M. A.; König, B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1486−1489. (g) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 6224−6233.

(9) Equey, O.; Alexakis, A. *Tetrahedron: Asymmetry* **2004**, *15*, 1531−1536.

(10) (a) Yadav, J. S.; Shekharam, T.; Srinivas, D. *Tetrahedron Lett.* **1992**, *33*, 7973−7976. (b) Yadav, J. S.; Shekharam, T.; Gadgil, V. R. *J. Chem. Soc., Chem. Commun.* **1990**, *11*, 843−844.

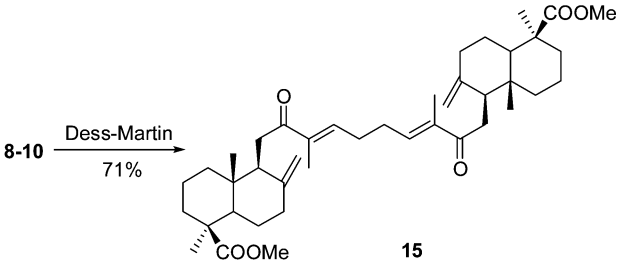
After analyzing these preliminary results, it seemed reasonable to anticipate that higher regioselectivities could be reached by increasing the degree of substitution of the carbons attached to the oxirane ring. Pleasingly, the coupling of epoxides **7**, methyl (12*R*,13*R* + 12*S*,13*S*)-12,13-epoxy-*trans*-communate (6:4 ratio), was found to be completely regioselective, leading to a 75% yield of diols **8** (12*R*,12′*R*), **9** (12*R*,12′*S*), and **10** (12*S*,12′*S*) (entry 5, Scheme 3). Only *E* olefins were obtained. Similar results were obtained when epoxides **11**, methyl (12*R*,13*S* + 12*S*,13*R*)-12,13-epoxy-*cis*-communate (57:43 ratio), were made to react under identical conditions, with a 72% yield of diols **8**−**10** being isolated (entry 6). Diols **8**−**10** were made to converge easily to the same diketone, **15**, by oxidation with Dess−Martin periodinane at a yield of 71% (Scheme 4). Compounds **8**−**10** and **15** can be considered analogues of natural onoceranes with potential bioactivity.[11]

Scheme 3[a]



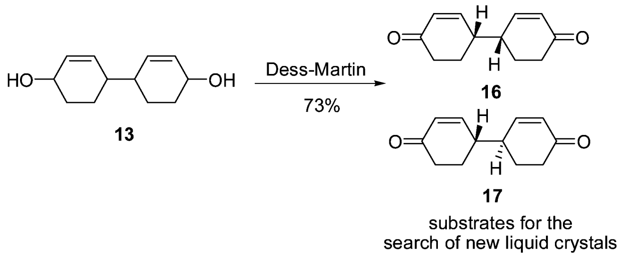
[a] Together with **1**, **5**, and **13**, the corresponding γ,α′ regioisomers **3**, **6**, and **14** were also obtained (cf. Table 1 for proportions).

Scheme 4



When the reaction was made with cyclic vinylepoxide **12**, diol **13** was obtained as major compound (as a mixture of diastereomers) (entry 13). There was also a decrease in the regioselectivity of the homocoupling process compared to the results found with acyclic epoxides. The formation of **13** is of additional interest because its oxidation leads satisfactorily to ketones **16** and **17** (1:1), which have been used as the starting substrate in the search of liquid crystals (Scheme 5).[12]

Scheme 5



These results are in agreement with the mechanisms proposed in pathway (b) of Scheme 2. This proposal involves either an η^1-allyltitanium species (**II**),[13] which would be added to the starting oxirane via a S_N2' process, or a dimerization of the intermediate allylic radical (**I**). The following experimental data were taken into account to decide between the two possible pathways. Changes in the concentration of the starting material, **2**, do not affect the outcome of the reaction to any significant degree (entries 7 and 8). Furthermore, when **2** is treated with Ti(III) in the presence of the radical trap acrylonitrile, no additional products were detected (entry 9).

Additionally, the reductions of vinylepoxides reported by Yadav et al. can also be attributed to the participation of allyltitanium intermediates. All of the above seems to indicate that the allyltitanium species is likely to be the intermediate involved in these coupling processes, although a dimerization of the intermediate allylic radical **I** should not be ruled out. Thus, a catalytic cycle justifying the regeneration of the Ti(III) reagent is shown in Scheme 6.

Bearing in mind that an increase in the degree of substitution on the oxirane favors the existence of the species **IIb** (possessing *E* stereochemistry), a type **V** intermediate, involving an intermolecular association between the allyltitanium species and the starting vinylepoxide (Scheme 7), may well account for the observed γ,γ′ regioselectivity and *E*,*E* diastereoselectivity. In **V**, the substituent R_1 must adopt an axial orientation to allow the proposed chairlike geometry, which explains satisfactorily the complete diastereoselectivity toward *E* olefins that we found. Furthermore, the similarity of the results obtained with the diastereomeric 12,13-epoxides **7** or **11** (entries 5 and 6) supports the existence of this intermediate.

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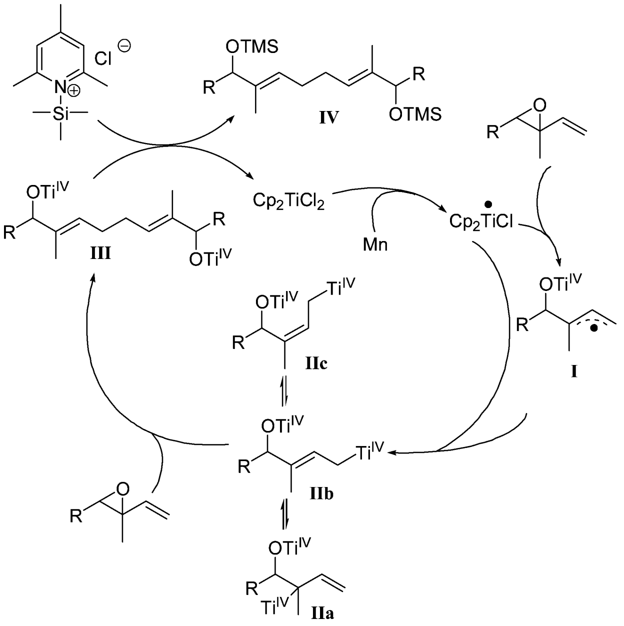
(11) Orhan, I.; Terzioglu, S.; Sener, B. *Planta Med.* **2003**, *69*, 265−267.

(12) Hoffmann, R. W.; Brandl, T.; Kirsch, P.; Harmas, K. *Synlett* **2001**, 960−963.

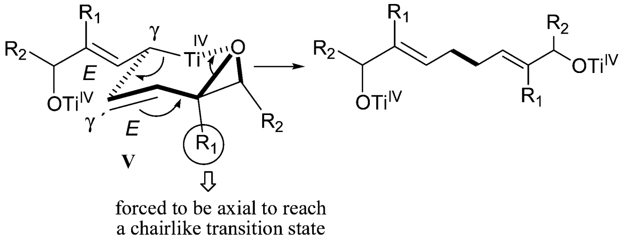
(13) Existence of η^1-allyltitanium species in equillibrium has been postulated previously: Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881−3882.

Scheme 6



The satisfactory results obtained when **2**, **7**, and **11** were used as substrates for coupling prompted us to test the feasibility of achieving this process while lowering the quantities of Cp_2TiCl_2 and Mn used. In the case of **2**, when the quantity of titanium was reduced 20 times, only a slight decrease of the reaction rate was noted but yields remained similar (entry 10). Comparable results were found when the quantity of Mn was reduced by half (entry 11). Similarly, when epoxides **11** were treated with 0.01 equiv of Cp_2TiCl and 8 equiv of Mn, 75% of the corresponding γ,γ' coupling products was obtained (entry 12). We believe that the repetition of results when the quantity of reagents is notably reduced increases the potential interest of this protocol.

Scheme 7



In summary, the reduction of vinyloxiranes with Cp_2TiCl resulted in good-to-excellent yields of homocoupling products and good control of the regio- and diastereoselectivity of the process was maintained in most cases. This is a completely novel carbon−carbon bond-forming reaction compatible with a number of functional groups. The process leads to the rapid, efficient formation of highly-functionalized intermediates for the synthesis of organic compounds such as **1** and **13** or new hybrids of natural products such as homoonoceranes.

Acknowledgment. This research was supported by the Spanish Ministry of Science and Technology. Project BQU 2002-03211. Thanks go to our colleague Dr. J. Trout for revising our English text.

Supporting Information Available: Experimental procedures and spectroscopic data of new compounds and ^1H and ^{13}C NMR spectra of **1**, **3**, **5**−**10**, **12**, **13**, and **15**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052849W